

EXHIBIT B

Health Policy Review

Reframing the Prevention Strategies of the Opioid Crisis: Focusing on Prescription Opioids, Fentanyl, and Heroin Epidemic

Laxmaiah Manchikanti, MD¹, Jaya Sanapati, MD², Ramsin M. Benyamin, MD³, Sairam Atluri, MD⁴, Alan D. Kaye, MD, PhD⁵, and Joshua A. Hirsch, MD⁶

From: ¹Pain Management Center of Paducah, Paducah, KY;

²University Pain Medicine and Rehabilitation Center, Newark, NJ; ³Millennium Pain Center, Bloomington, IL; ⁴Tri-State Spine Care Institute, Cincinnati, OH;

⁵LSU Health Science Center, New Orleans, LA; ⁶Massachusetts General Hospital and Harvard Medical School, Boston, MA

Address Correspondence:
Laxmaiah Manchikanti, MD
Pain Management Center of Paducah

2831 Lone Oak Road
Paducah, Kentucky 42003

E-mail: drlm@thepainrmd.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-20-2018

Accepted for publication:
07-10-2018

Free full manuscript:
www.painphysicianjournal.com

The opioid epidemic has been called the “most consequential preventable public health problem in the United States.” Though there is wide recognition of the role of prescription opioids in the epidemic, evidence has shown that heroin and synthetic opioids contribute to the majority of opioid overdose deaths. It is essential to reframe the preventive strategies in place against the opioid crisis with attention to factors surrounding the illicit use of fentanyl and heroin.

Data on opioid overdose deaths shows 42,000 deaths in 2016. Of these, synthetic opioids other than methadone were responsible for over 20,000, heroin for over 15,000, and natural and semi-synthetic opioids other than methadone responsible for over 14,000. Fentanyl deaths increased 520% from 2009 to 2016 (increased by 87.7% annually between 2013 and 2016), and heroin deaths increased 533% from 2000 to 2016. Prescription opioid deaths increased by 18% overall between 2009 and 2016.

The Drug Enforcement Administration (DEA) mandated reductions in opioid production by 25% in 2017 and 20% in 2018. The number of prescriptions for opioids declined significantly from 252 million in 2013 to 196 million in 2017 (9% annual decline over this period), falling below the number of prescriptions in 2006. In addition, data from 2017 shows significant reductions in the milligram equivalence of morphine by 12.2% and in the number of patients receiving high dose opioids by 16.1%.

This manuscript describes the escalation of opioid use in the United States, discussing the roles played by drug manufacturers and distributors, liberalization by the DEA, the Food and Drug Administration (FDA), licensure boards and legislatures, poor science, and misuse of evidence-based medicine. Moreover, we describe how the influence of pharma, improper advocacy by physician groups, and the promotion of literature considered peer-reviewed led to the explosive use of illicit drugs arising from the issues surrounding prescription opioids.

This manuscript describes a 3-tier approach presented to Congress. Tier 1 includes an aggressive education campaign geared toward the public, physicians, and patients. Tier 2 includes facilitation of easier access to non-opioid techniques and the establishment of a National All Schedules Prescription Electronic Reporting Act (NASPER). Finally, Tier 3 focuses on making buprenorphine more available for chronic pain management as well as for medication-assisted treatment.

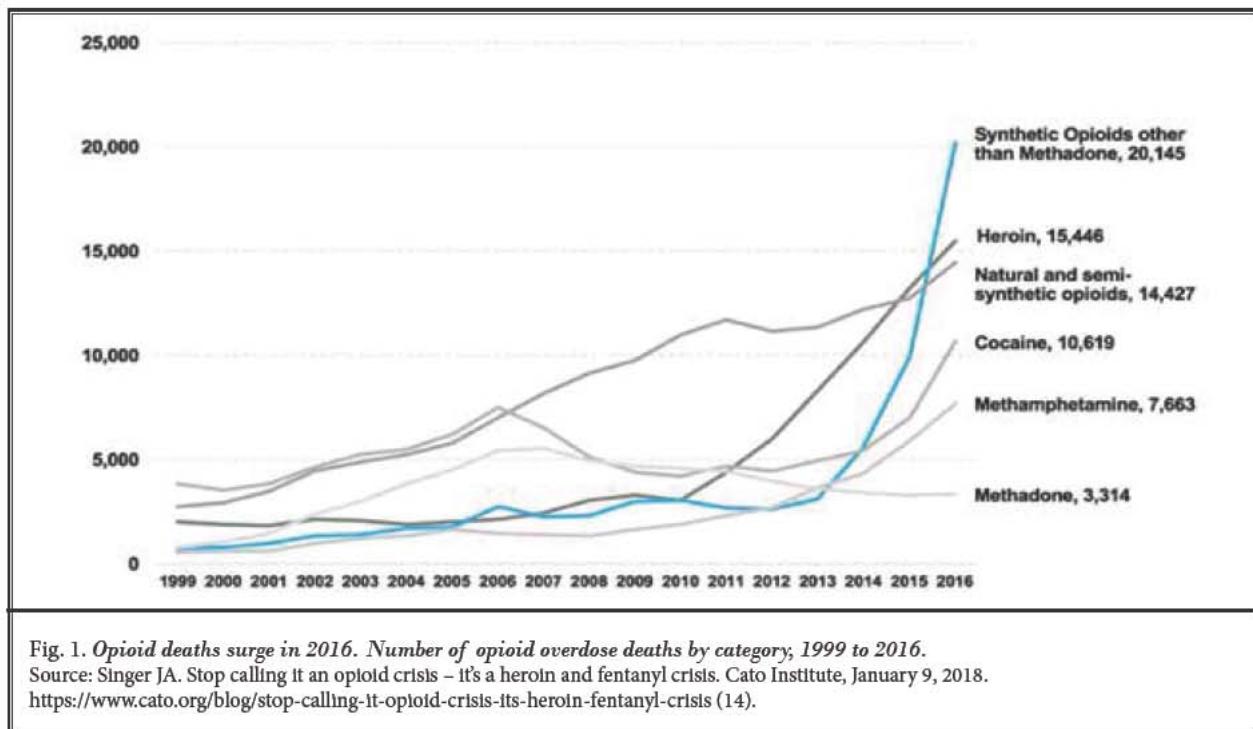
Key words: Opioid epidemic, fentanyl and heroin epidemic, prescription opioids, National All Schedules Prescription Electronic Reporting Act (NASPER), Prescription Drug Monitoring Programs (PDMPs)

Pain Physician 2018: 21:309-326

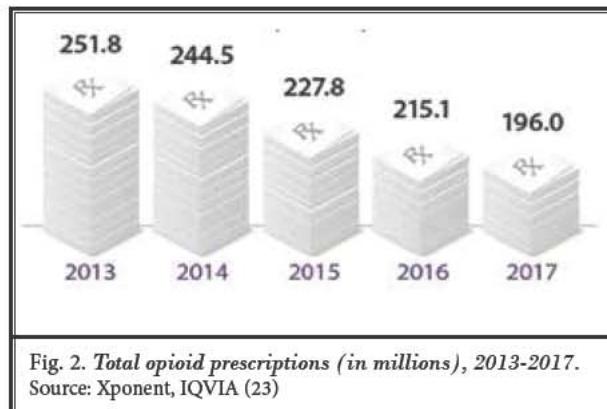
Opoid abuse is among the most consequential, and sadly, preventable public health threats facing the nation (1-13), with recent authority and news reports of 115 deaths per day due to opioids.

It is important to note that this statistic includes all opioid-related deaths - the majority due to fentanyl and heroin (5,8,14-16). President Trump has framed the opioid epidemic as a national emergency. The US

Pain Physician: July/August 2018: 21:309-326

Fig. 1. *Opioid deaths surge in 2016. Number of opioid overdose deaths by category, 1999 to 2016.*

Source: Singler JA. Stop calling it an opioid crisis – it's a heroin and fentanyl crisis. Cato Institute, January 9, 2018.
<https://www.cato.org/blog/stop-calling-it-opioid-crisis-its-heroin-fentanyl-crisis> (14).

Fig. 2. *Total opioid prescriptions (in millions), 2013-2017.*
Source: Xponent, IQVIA (23)

Department of Health and Human Services (HHS) and various organizations, including the National Institutes of Health (NIH), Food and Drug Administration (FDA), and Drug Enforcement Administration (DEA) aim to fight the opioid epidemic with science and regulation. The U.S. Congress and state and local authorities have focused enormous resources on this issue (1,2,5,7-11,14-16). However, with changing public opinion and enormous visibility, this concern stems from the magnitude of opioid-related deaths reached in 2016, when more than 11 million Americans misused prescription opioids and overall drug overdose deaths

in 2016 contributed to over 64,000 deaths with 42,249 due to opioids – 20,145 associated with synthetic opioids other than methadone, 15,446 from heroin, 14,427 from natural and semi-synthetic opioids or prescription opioids, and 3,314 from methadone. In comparison, in 2016, cocaine overdose caused 10,619 deaths and methamphetamine 7,663 deaths as shown in Fig. 1 (5,11,14-16).

Data shows that illicit fentanyl contributed to almost 50% of the deaths in 2016, whereas overall prescription opioid deaths without fentanyl or heroin but including other illicit drugs may have contributed to less than 8,000 in 2016 with methadone contributing to 3,314 deaths despite methadone prescriptions representing only 1% of total opioid prescriptions. In addition to the reduced production mandated by DEA (25% reduction in 2017, 20% in 2018) data shows a decline in total prescriptions and overall dosages, starting from 2013 with a reduction from 252 million opioid prescriptions in 2013 to 196 million in 2017 (annual decrease by 9%) as shown in Fig. 2 (15-23). In fact, data from 2016-2017 showed a decrease by 23.3 billion in morphine milligram equivalents (MMEs) dispensed to patients on a volume basis, with a 12.2% decrease in prescriptions, and a 16.1% decline in patients receiving high doses (> 90 MMEs per day) as shown in Fig. 4. It is

Reframing the Prevention Strategies of the Opioid Crisis

postulated that further declines will occur throughout 2018. However, the decline in opioid prescription rate is not accompanied by a correlating decline in opioid abuse and death rate (Figs. 3 and 4) (23).

In an analysis of deaths and years of life lost with percentage change, from the 25 leading causes of death in the United States from 1990-2016, opioid use disorders ranked 52 in 1990, moved up to 15 in 2010, and remained at 15 in 2016 (24,25). However, in terms of years lived with disability (YLDs), opioid use disorders

ranked 7 in 1990 and 2010 and moved down to 8 in 2016, showing very little improvement over the years (24,25). It is now known that many deaths due to illicit fentanyl and heroin have been counted as prescription opioid deaths because of the inability to separate fentanyl formulation and metabolites of heroin (22). In addition, fentanyl deaths increased 520% from 2009 to 2016 at an annual rate of 87.7% from 2013 to 2016, whereas heroin deaths increased 533% from 2000 to 2016 (14-16). In fact, from 2015 to 2016, deaths attrib-

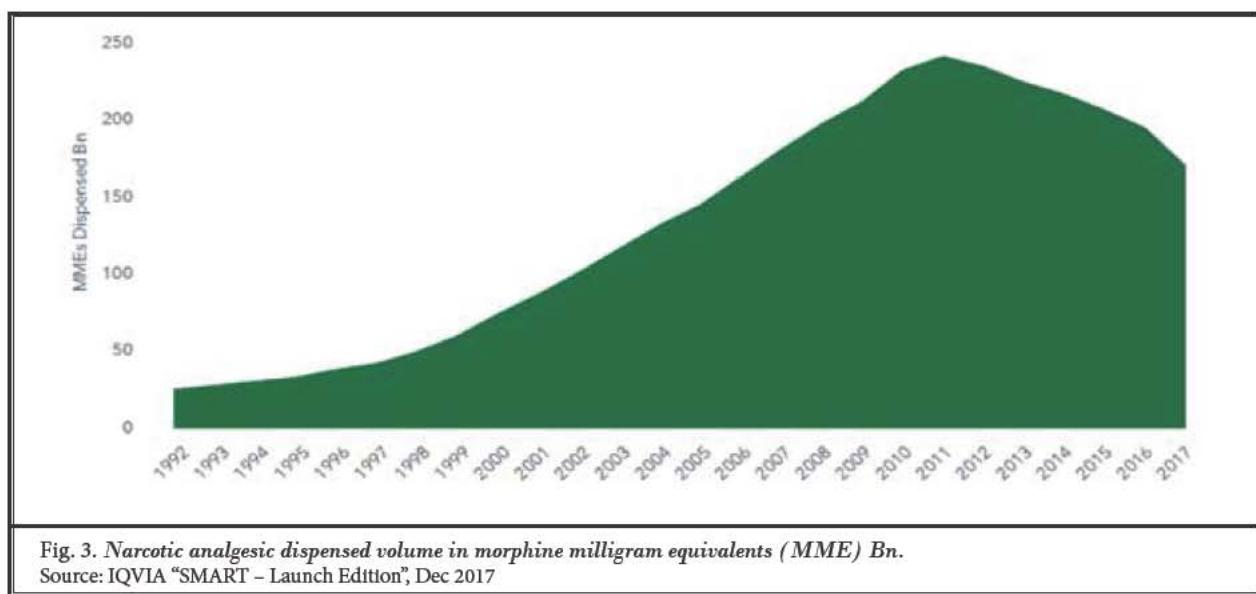


Fig. 3. Narcotic analgesic dispensed volume in morphine milligram equivalents (MME) Bn.
Source: IQVIA "SMART - Launch Edition", Dec 2017

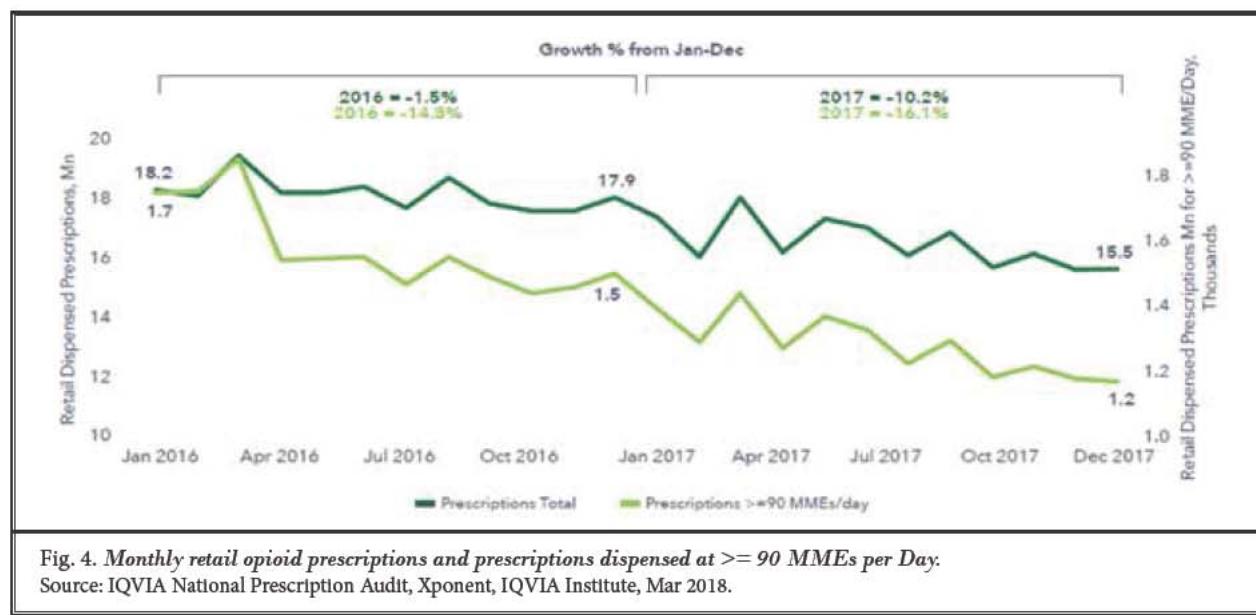
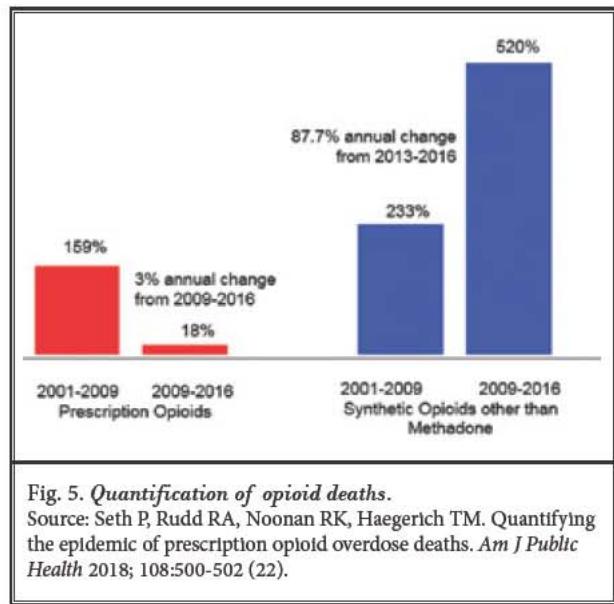


Fig. 4. Monthly retail opioid prescriptions and prescriptions dispensed at ≥ 90 MMEs per Day.
Source: IQVIA National Prescription Audit, Xponent, IQVIA Institute, Mar 2018.



uted to illicitly manufactured fentanyl doubled from 10,000 to over 20,000 (5). This increase is enough to account for most of the increase in drug overdose deaths from 2015 to 2016 (5). The quantification of opioid deaths yields startling results as demonstrated in Fig. 5 (22). Prescription opioid deaths increased 18% at an annual rate of 3% from 2009 to 2016, in contrast to the earlier increase of 159% from 2001 to 2009. On the same token, synthetic opioids other than methadone, specifically illicit fentanyl, increased 520% from 2009 to 2016 at an annual rate of 87.7% from 2013 to 2016, following an increase by 233% from 2001 to 2009 (22).

The authorities and the public at large have appropriately focused on the opioid epidemic throughout its early years. Authors of this manuscript have argued strenuously for such consideration for some time (26-28). It is essential to move the discussion forward by examining the more nuanced culprits of fentanyl and heroin. This article thus focuses on reframing the opioid epidemic as a prescription opioid fentanyl and heroin epidemic with the need to establish effective strategies.

Public Opinion

Blendon and Benson (11), in a survey of public opinion on opioid-abuse epidemic, found that on a list of 15 possible 2017 priorities for Congress and the president, opioids ranked sixth, with 24% naming opioids an extremely important priority. The results of this survey also revealed that addiction to prescription pain medications was believed to be an illness by 53% and a per-

sonal weakness by 36% of surveyed patients. Further, public opinion on responsibility for the opioid crisis has been highly variable as evidenced by multiple surveys as shown in Table 1 and Fig. 6 (11,29,30). The results demonstrated that overall responsibility attributed to drug users varied from 10-29%, physicians 19-33%, drug companies 13-38%, and drug dealers 11-28%. In summary, it appears that in one survey, drug companies and distributors were considered the most responsible entities for the opioid crisis by 43% (30) followed by physicians in another survey by 33% (11), followed by 29% for drug users (29) and 28% for drug dealers (11).

EVOLUTION OF THE OPIOID EPIDEMIC

Opioids date back 5,000 years from the use of extracts of the poppy plant, named the "joy plant" for medicinal purposes (31). Numerous over-the-counter medicinal products from 1849 have used morphine, opium, heroin, and cocaine including a sleep aide and analgesic for children that contained 65 mg of morphine sulfate per ounce as shown in Table 2 (31). An alcohol-based tincture of 10% powdered opium called "laudanum", was widely used leading to the addiction of many in the United States (31). "Soldier's disease", an epidemic of addiction during the Civil War, was caused by morphine, isolated from opium about 50 years earlier (31,32). Ironically, Bayer Pharmaceuticals marketed heroin as an analgesic and claimed it was less addictive than other opioids, as early as 1874. There were similar claims about multiple other opioids as well as cocaine. Sadly, there were an estimated 200,000 heroin addicts in the United States by 1972 (31). The federal legislation starting with the Heroin Act (1906-1924), which outlawed production and possession of heroin, was a response to control escalating toll of drug abuse (31). The Controlled Substance Act (CSA) was established in 1970. The CSA regulated narcotic manufacturing and distribution and classified controlled substances into five narcotic schedules (33). By 1971, 15% of the soldiers in Vietnam had become heroin addicts. This led President Nixon to declare heroin "Public Enemy Number One" in 1972 and direct federal support toward the establishment of methadone clinics (34). However, methadone soon became a drug of abuse. Near the end of the century, the emergence of a new pain movement focused on under-treatment, the influence of the pharmaceutical industry, and the liberalization of multiple existing narcotics regulations contributed to the ensuing escalation in prescription opioid use, abuse, and overdose-related deaths (26,27).

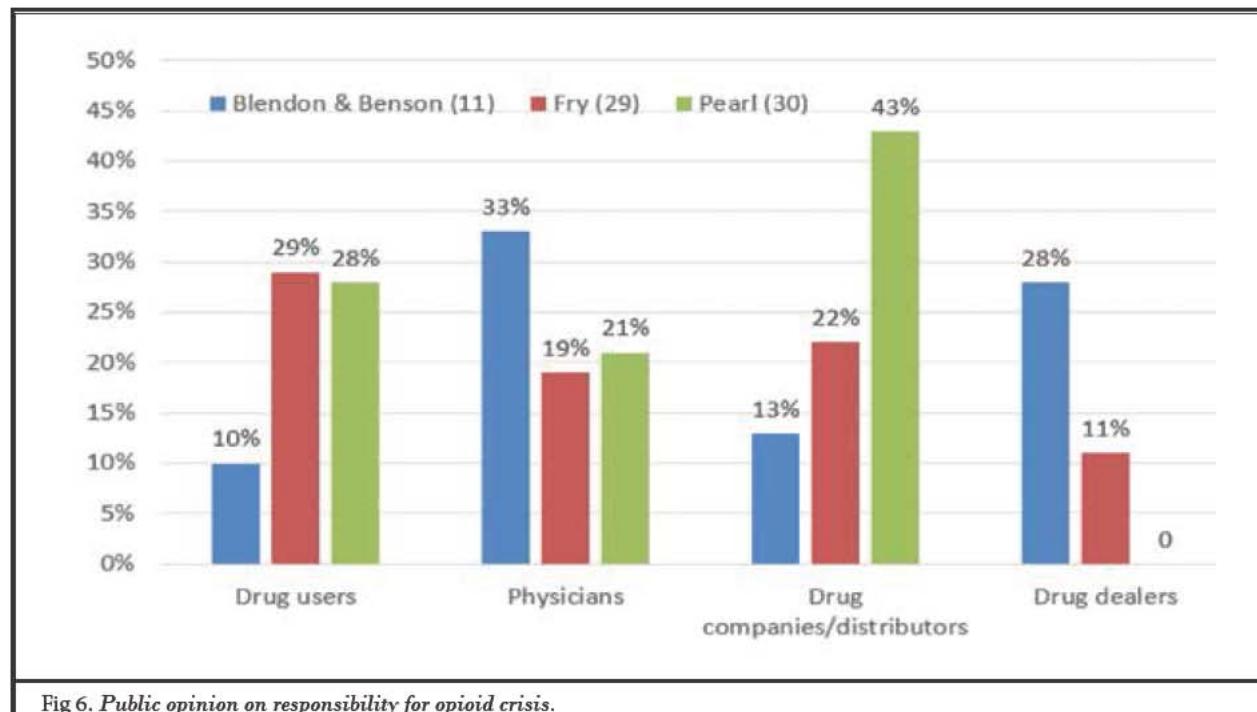
Reframing the Prevention Strategies of the Opioid Crisis

TRAGIC FAILURE OF SYSTEMS

Despite overwhelming evidence that the epidemic of opioid use involves the use of prescription opioids, fentanyl, and heroin, policy experts appear to have focused on prescription opioids as the main target in the U.S. (1,3-5,14,26-27,31). In this regard, despite overwhelming evidence of misinformation and misdeeds by drug manufacturers, drug dealers, drug distributors, and multiple agencies overseeing controlled substance activities, policymakers have targeted over-prescription by physicians to a disproportionate extent. Along with illicit fentanyl and heroin, prescription opioids continue to contribute to deaths, but at a significantly lower rate.

Table 1. *Public opinion on responsibility of opioid crisis.*

	Blendon & Benson (11)	Fry (29)	Pearl (30)
Drug users	10%	29%	28%
Physicians	33%	19%	21%
Drug companies/distributors	13%	22%	43%
Drug dealers	28%	11%	--
Elected officials/FDA	7%	--	--
Unknown/other	--	18%	--

Fig 6. *Public opinion on responsibility for opioid crisis.*Table 2. *Representative over the counter patented medicines and kits.*

Product	Content	Indication
Mrs. Winslow's Soothing Syrup Bangor, Maine (1849)	Morphine sulfate 65 mg/oz	Sleep aid and analgesic for children
Stickney and Poor's Pure Paregoric Use (1905)	Opium 18/16 gr/ounce in 46% alcohol	Asthma for patients 5 days old and up
Bayer & Company's-Heroin (1890)	Heroin 1/24 grain per pill and in elixirs	Antitussive
Vapor-Oil Treatment No. 6. National Vaporizers Co. Kalamazoo, MI (late 1800s)	Opium 35 mg/oz in alcohol	Asthma and "spasmodic affections"
Parke-Davis & Company's "Emergency Kit" (1894)	Cocaine, morphine, atropine, strychnine, and a hypodermic syringe	"Emergencies"

Source: deShazo R, Johnson M, Eriator I, Rodenmeyer K. Backstories on the U.S. opioid epidemic good intentions gone bad, an industry gone rogue and watch dogs gone to sleep. Am J Med 2018 [Epub ahead of print] (31).

The confluence of the emergence of the influence of pharma and the death of evidence-based medicine originated with the Sackler brothers (31-35). The Sackler brothers, three psychiatrists, purchased Purdue Frederick Pharma in 1952 with an initial focus on laxatives and earwax. The company shifted its focus to pain management and released MS Contin in 1984. Subsequently, in 1996, OxyContin was released. Dr. Arthur Sackler, who died in 1987, had become a wealthy pharmaceutical marketing executive, publisher of medical trade publications, and father of direct to physician marketing (31,35-37). Arthur Sackler started MD Publications in the 1960s and promoted diazepam and chlordiazepoxide (Librium®), which led to over 100 million prescriptions per year by 1973. He infamously paid \$300,000.00 to recruit Henry Welch, MD from the FDA to promote MD Publications.

OxyContin was falsely marketed as an opioid with low addiction potential based on a 1980 New England Journal of Medicine letter to the editor that claimed that under 1% of patients discharged on narcotics from the author's hospital developed addiction (38). Lavish trips and stipends for marketing influenced physicians to prescribe OxyContin. In addition, Purdue Pharmaceutical employed a large aggressive sales force, offered a free 30-day supply of OxyContin, and promoted the theory of pseudo-addiction suggesting that more medication is required as patients hurt more (35-38). With the support of multiple pain organizations, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the Veterans Health Administration (VHA), and other proactive groups, prescription of OxyContin and other opioids exploded (35-52).

The Pain Movement with Confluence of Interest

Houde, Foley, and Portenoy led the way for opioid explosion through their academic stature and leadership positions in the American Pain Society (APS) (31, 39,53). Portenoy and Foley advocated that opioid maintenance therapy for chronic non-cancer pain was safe and humane based on a report of 38 cases (39). The APS held the mantle as the advocacy group for opioid treatment of pain. It received much of its support from Purdue Pharma. It also promoted opioids as a management option in chronic low back pain publications (54). The APS advocated the establishment of pain as the "fifth vital sign" in 1995. The APS and American Academy of Pain Medicine (AAPM) published a consensus statement in 1997 declaring evidence of addiction due to

the appropriate prescription of opioids insufficient (41). In 2010, the International Association for the Study of Pain (IASP) contributed a patients' rights component to the ongoing pain movement declaring patient's entitlement to access pain management treatments, including opioids (41). The Veterans Affairs (VA) medical system, the Joint Commission (JCAHO), the American Medical Association (AMA), the American Academy of Family Physicians (AAFP), a number of pain organizations funded by Purdue Pharma, and many patient advocacy groups gathered in support of pain as the fifth vital sign (42-45). The fifth vital sign was eventually withdrawn in 2016 after its contributions to the opioid epidemic were recognized (43,45). JCAHO continues to establish new measures that are similar to pain as the fifth vital sign. In addition, multiple organizations advocating opioids for pain management successfully lobbied the US Congress to declare a decade of pain control and research in 2000 (41). Another crucial event was the official implementation of pharma-developed opioid prescription policies in 2002 through the University of Wisconsin, Madison Pain Policy Study Group (PPSG), which received \$2.5 million in grants from the industry with Purdue Pharma alone contributing \$1.6 million (31,46). The Federation of State Medical Boards (FSMB) adapted the PPSG 2002 policies to produce a document entitled "Update and clarify state medical board policies on the use of opioid analgesics to treat pain" sent to medical licensure boards (47). This report and policy model essentially unleashed opioid prescription patterns to ensure that physicians could not be sanctioned based on the dose or frequency of opioids prescribed for legitimate medical purposes as defined in the liberated 1970 Narcotics Control Act. This report has since become a cornerstone (no dose threshold) of pill mills during the explosion of the prescription opioid epidemic. Purdue Pharma provided \$100,000 for the printing of 300,000 widely distributed copies of the FSMB model guidelines, which had been based on a single observational study by Portenoy in addition to expert opinions (39,40). The guidelines were developed not only with extensive bias and conflicts of interest but also in the absence of high-quality scientific studies (48). Figure 7 shows organizational contributions made by opioid manufacturers from 2012 to March 2017 (55). Earlier contributions were published in 2012 (56).

DRASTIC FAILURES IN OVERSIGHT

Over the years, drastic failures have occurred in oversight of not only opioid manufacturing, distribution, diversion, and import but also the medical

Reframing the Prevention Strategies of the Opioid Crisis



Fig. 7. Recipients of opioid manufacturer funding: Purdue, Janssen, Insys, Depomed, and Mylan payments from January 2012 to March 2017.

Source: United States Senate Committee on Homeland Security and Governmental Affairs (55)

necessity and appropriate monitoring of opioid prescriptions. The Controlled Substance Act (CSA) of 1970 (33) essentially relaxed the anti-opioid portions of the Harrison Narcotics Tax Act of 1914 by outlining a legitimate medical purpose for opioids (33): this would lead the path towards later oversight failures. The CSA also established the US Drug Enforcement Agency to set production quotas and to monitor and control diversion and excessive production of narcotics (50). The DEA was founded as an agency of the Department of Justice in July 1973 with the mission to combat drug smuggling and use within the United States. Without foreseeing the subsequent and obviously unintended consequences, the DEA joined 21 health care organizations in 2001 to call for improved approaches to assure that prescription opioids were available for medical use and shielded from diversion (51). During this time, the provider community held a multitude of negative opinions of the DEA, and ASIPP was introducing its first version of the National All Schedules Prescription Electronic Reporting Act (NASPER) (52).

Between 1996 and 2007, the DEA increased US production of opioids by 10-fold for fentanyl, 4-fold for hydrocodone, and 4.5-fold for hydromorphone. By 2007, it had just begun to establish quotas for OxyContin. Despite the extensive criticism it received for laxity

on opioid prescribing regulation, the DEA sanctioned less than 0.1% of physicians for opioid prescribing violations from 1999 to 2003 (51,53).

In 2016, President Obama signed into law the Ensuring Patient Access and Effective Drug Enforcement Act, also known as the Marino Act. The act was described as "the crowning achievement of a multifaceted campaign of the drug industry to weaken the DEA enforcement activities against drug distribution companies that were supplying corrupt physicians and pharmacies who pedal narcotics on the black market" (57). The Marino Act led to the closure of the DEA's Special Operations Unit, which faced congressional criticism after the unit was found to have covertly collected internal phone records to monitor drug traffic (57,58).

The FDA also made substantial unintentional contributions to the opioid epidemic. The FDA approval of OxyContin in 1995 is considered to have played a key role in one of the greatest medical disasters in U.S. history (31,35,36,59). In 1995, Dr. Curtis Wright, team medical review officer for the FDA, recommended approval of Purdue Pharma's OxyContin for moderate to severe pain. In an October 16, 1995 report for the FDA, Dr. Wright wrote the following: "...care should be taken to limit competitive production [of OxyContin]," two years before he began working for Purdue Pharma.

Dr. David Kessler, FDA commissioner at the time OxyContin was approved, acknowledged, "no doubt it was a mistake. It was certainly one of the worst medical mistakes, a major mistake." It was also reported that a Purdue Pharma promotional video featuring success stories of patients treated for chronic pain with OxyContin included several patients who later died or became addicted to the drug (56).

The FDA approved Opana® (oxymorphone) in 2006 despite a past history of oxymorphone abuse in the 1960s and 1970s resulting in the drug's removal from the market (56). In 1995, the FDA approved tramadol as a non-controlled analgesic despite prior research indicating the drug's potential to be abused when it first arrived on the U.S. market (60). The FDA also approved Zohydro (a hydrocodone product) on October 25, 2013, against the recommendation of the FDA's own appointed scientific advisory panel, which voted 11 to 12 against the approval (61). Further, the approval of Zohydro was supported by FDA commissioner Margaret Hamburg, who cited the Institute of Medicine's statistics on chronic pain, including which were exaggerated and misleading (61). Hamburg spoke of "100 million Americans suffering from severe chronic pain," which became a central part of the debate used to justify Zohydro's approval (61-63).

Among the multiple oversight agencies, boards of medical licensures governed by each state legislature,

but also following unofficial mandate from Federation, have fueled the opioid epidemic with misinformation to physicians (46,47).

Industry

In comparison to prior drug industry contributions made to influence guidelines and promote products (31,46,55-57), recent publications from the Senate show similar patterns, with \$9 million funneled to the leading pain treatment advocacy organizations and industry groups (Fig. 7), that allegedly shaped policy and public opinion around opioids. Charitable funding from the Sackler family for numerous organizations and educational institutions has also recently come under attack (35,36). In fact, Marissa Sackler, daughter of Raymond Sackler, commented, "philanthropy is old fashioned – it is social entrepreneurship." The Ensuring Patient Access and Effective Drug Enforcement Act (HR-4709), often referred to as the Marino Act, received lobbying expenses of over \$100 million from pharmaceutical companies over 2014-2016 (57). The Marino Act made it virtually impossible for the DEA to freeze suspicious narcotic shipments from distributors (57-59). Joseph Rannazzisi, former head of the DEA's Office of Diversion Control notably influential in closing pill mills in multiple Florida jurisdictions, commented, "The drug industry, the manufacturers, wholesalers, distributors, and chain drugstores have an influence over Congress that has never been seen before," regarding the Marino Act. John J. Mulrooney II, DEA Chief Administrative Law Judge, commented, "At a time when by all accounts, opioid abuse, addiction, and deaths were increasing markedly," the Marino Act "imposed a dramatic diminution of the agency's authority (57)."

THE TRUE EPIDEMIC

OxyContin was reformulated to become more difficult to abuse in 2010. Ostensibly, reformulation reduced non-medical use and abuse, but a spike in heroin users followed (35,36,64-66). Mexico is the largest source of heroin used in the United States. The increasing demand for heroin in the early 1970s resulted in the emergence of a new breed of Mexican drug cartels producing "black tar heroin" (31) (Fig. 8). Coupled with the increase in heroin abuse was the introduction of fentanyl, an opioid 80 times more potent than heroin first marketed in the United States as Duragesic in the 1990s (67). Drug dealers began adding fentanyl to heroin for a more potent effect. Of note, in 2016, fentanyl was involved in half of all overdose deaths in Illinois

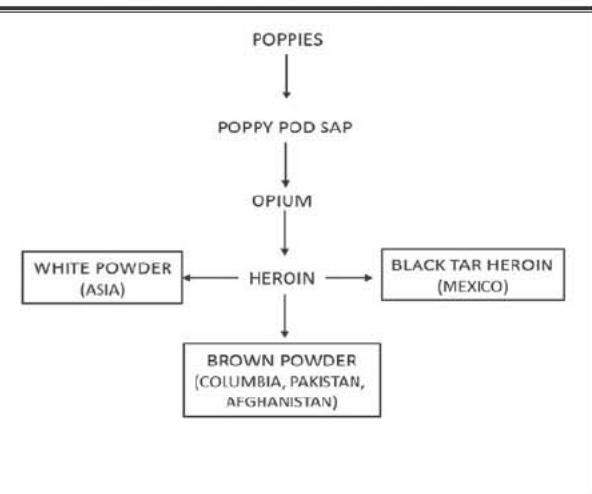


Fig. 8. Historical production and geographic sources of heroin.

Source: deShazo R, Johnson M, Eriator I, Rodenmeyer K. Backstories on the U.S. opioid epidemic good intentions gone bad, an industry gone rogue and watch dogs gone to sleep. *Am J Med* 2018 [Epub ahead of print] (32).

Reframing the Prevention Strategies of the Opioid Crisis

(68). United States drug companies took measures to curtail fentanyl overproduction. Around this time, China began to produce large quantities of fentanyl and develop fentanyl derivatives sold to heroin producers in Mexico and drug users in the United States (31). In addition, carfentanil, an elephant tranquilizer 100 times more potent than fentanyl -- essentially 8,000 times more potent than heroin -- led to overdoses in Ohio, New York, Pennsylvania, Florida, and neighboring states (69,70).

Table 3 outlines the many factors that contributed to the opioid crisis, throughout which multiple states have sued drug companies and reached large settlements and awards.

In recent years, prescription opioid usage has decreased with the development of a multitude of federal, state, and local regulations. Regulations limiting opioid prescriptions for acute pain to 3-to-10 days courses have somewhat reduced the supply of prescription opioids available for non-medical use. CDC guidelines have included dose recommendations for prescribing opioids in primary care. In many jurisdictions, these guidelines have become regulations across specialties, including chronic pain management. The combined prescription of opioids and benzodiazepines has also declined following an FDA black box warning in 2016 (70).

DISCORDANCE: CURBING THE EPIDEMIC OR DENYING THE TREATMENT?

Here, we present divergent views on the opioid epidemic and the rise of heroin in conjunction with fentanyl.

According to Andrew Kolodny, founder of Physicians for Responsible Opioid Prescribing (PROP), most opioid overdose deaths had involved prescription opioids until 2011. Then, as prescription overdose deaths leveled off, deaths involving heroin began to soar. Kolodny considers the belief that a 2011 federal government crackdown on painkillers was responsible for many prescription drug abusers' switch to heroin a common misconception. Though a slowdown in opioid prescription may have occurred around 2011, oxycodone consumption has remained higher on a milligram per capita scale in the United States than in other developed countries, as shown in Figure 9. Lack of physician discipline in avoiding over-prescription played a significant role, but it was ease of access that had already influenced the vast majority of people who'd started using heroin after 1995 to make the switch

from prescription opioids. A sharp increase in overdose deaths occurred in 2011 in part because of the increasing illicit use of fentanyl, an inexpensive but potent synthetic opioid that was often mixed with or sold as heroin. Once medical examiners began to routinely test heroin overdose victims for the presence of fentanyl in 2013, an alarming trend in the identification of fentanyl as a cause of overdose deaths appeared. Data in 2016 indicated deaths from fentanyl reached 20,000, thus surpassing deaths from prescription opioids and heroin.

According to Josh Bloom of the American Council on Science and Health, nonmedical use of OxyContin started declining after the introduction of reformulated Oxycodone ER in 2010, pushing patients to heroin as shown in Fig. 10. Figure 10B shows escalating deaths due to heroin overdose following 2010. Further, Fig. 11 compares national overdose deaths from prescription opioid pain relievers (Fig. 11A), which stayed stable with slight increases as heroin deaths escalated as shown in Fig. 11B (66).

Figures 1 and 5 show the quantification of opioid death rates from 2001–2016. From 2001–2009, prescription opioid deaths increased by 159%, and deaths due to synthetic opioids other than methadone increased 233%. The rise in deaths from prescription opioids was slower from 2009 to 2016, over which prescription opioid deaths increased 18% overall at an annual rate of 3%. By contrast, from 2013 to 2016, synthetic opioids other than methadone increased 520% overall, 87.7% annually, fentanyl deaths topping in 2016 with over 20,000 deaths (71-74).

Figures 12-14 show that alongside the rise in drug-related deaths from 2009-2016 occurred a decrease in the utilization of multiple lumbar interventional techniques, including epidurals, percutaneous adhesiolysis, and lumbar facet joint nerve blocks. This decrease occurred despite the promotion of interventional pain procedures by multiple agencies and despite the availability of data from high quality randomized controlled trials that had undergone systematic reviews and cost-utility analysis (75-108).

REFRAMING THE PREVENTION STRATEGIES

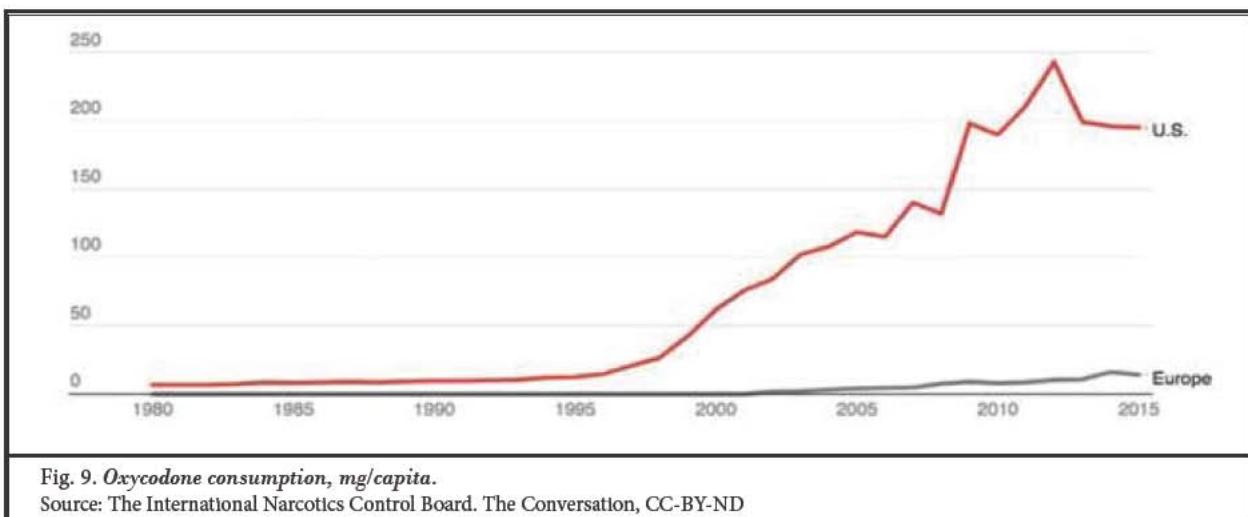
Over the past two decades, the American Society of Interventional Pain Physicians (ASIPP) has offered extensive pain management continuing education resources and received recognition by Congress and the Administration as a political action committee. ASIPP began issuing warnings and offering preventive measures in early 2000 with its proposal of a national program – the

Pain Physician: July/August 2018: 21:309-326

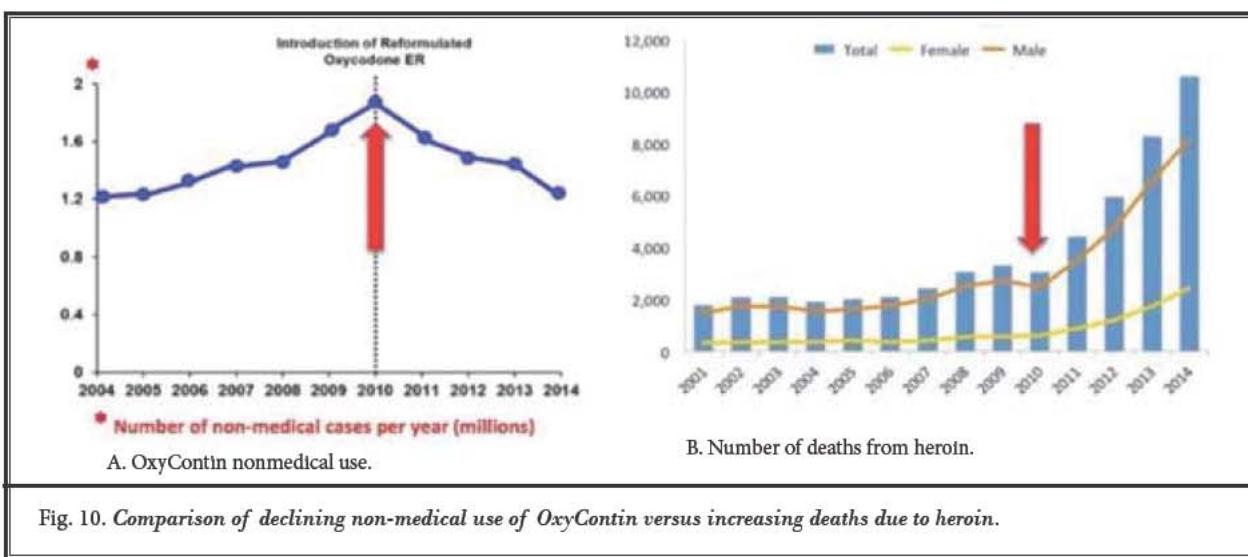
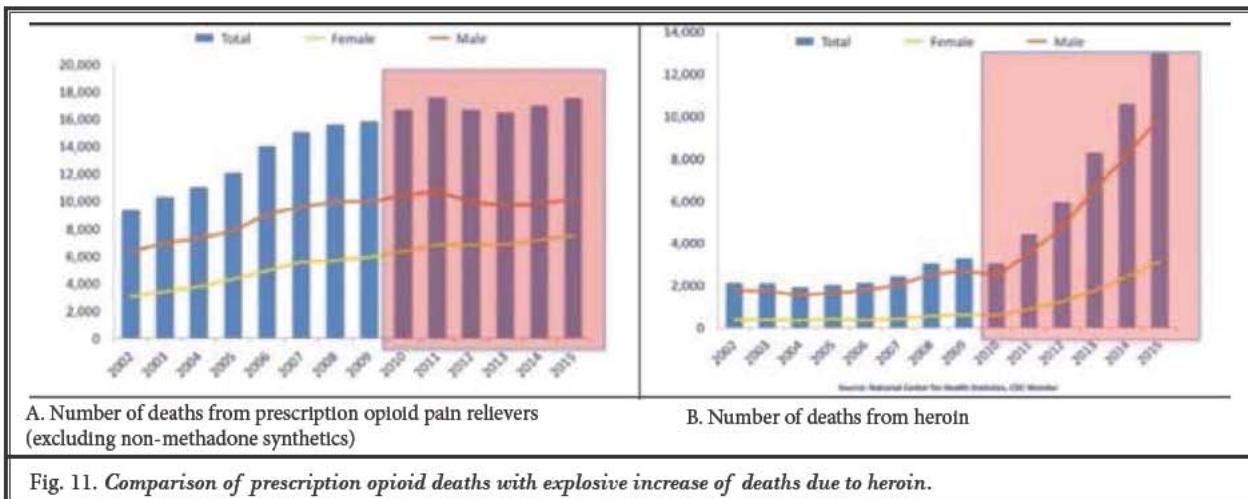
Table 3. *Factors promoting escalation of opioid use in United States.*

Drug Manufacturing and Distribution
• Corporate greed
• Lax regulations by FDA
• Removal of DEA authority by Marino Act
• Approval of OxyContin and Zohydro
• Supply chain without checks and balances
• Increased levels of production
• Direct to physician marketing
• False marketing claims about addiction to new, longer acting opioids
• False marketing claims of safety and efficacy of abuse resistant opioids
• Misrepresentation of the evidence of efficacy and lack of addiction
Liberalization (DEA, FDA, Licensure boards, Legislature)
• Controlled Substance Act essentially nullifying 1914 Harrison Narcotic Tax Act
• Approval of OxyContin and Zohydro
• Call for improved approaches to assure the availability of opioids by 21 health care organizations and supported by the DEA in 2001
• Federation of State Medical Boards (FSMB) recommendations to states with no disciplinary action against practitioner based solely on the quantity and/or frequency of the opioids prescribed: no dosing threshold
• Efforts by physician groups to better manage chronic pain
• Promotion of pain as a fifth vital sign
• Right to pain relief by IASP fifth vital sign by APS supported by AMA, AAFP, VA, JCAHO, AAAHC
• Right to pain relief act by legislatures
• Direct to physician marketing with poor science and misinformation
• Passage of Ensuring Patient Access and Effective Drug Enforcement Act (HR-4709) in 2016 weakening and essentially eliminating the DEA enforcement activities against corrupt activities of drug distribution companies
Poor Science
• Non-addictive based on a letter to the editor published in the New England Journal of Medicine.
• Portenoy's observational study of 38 patients promoting opioids for chronic noncancer pain
• Wisconsin Pain Policy Group developing the guidance without scientific evidence, promoted as state regulations
• Invention and promotion of pseudoaddiction and breakthrough pain
• Implementation of IMPAACT to promote positive opioid research
• 1997 joint statement by APS and AAPM of opioid use as safe in managing chronic noncancer pain
• Promotional material from drug industry considered as peer reviewed literature
• Approval of OxyContin and Zohydro
• False marketing claims of safety
• Creation of "Opiophobics"
Physicians and Promotion of Literature Considered as Peer Reviewed Literature
• Lack of physician education on the use of drugs with high abuse potentials
• Literature provided by the Pharma without differentiation of peer-reviewed literature versus marketing
• Direct to physician marketing
• Shared decision making based on patient demands or doctor's routine
• To obtain improved satisfaction and revenues
• Provider run pill mills

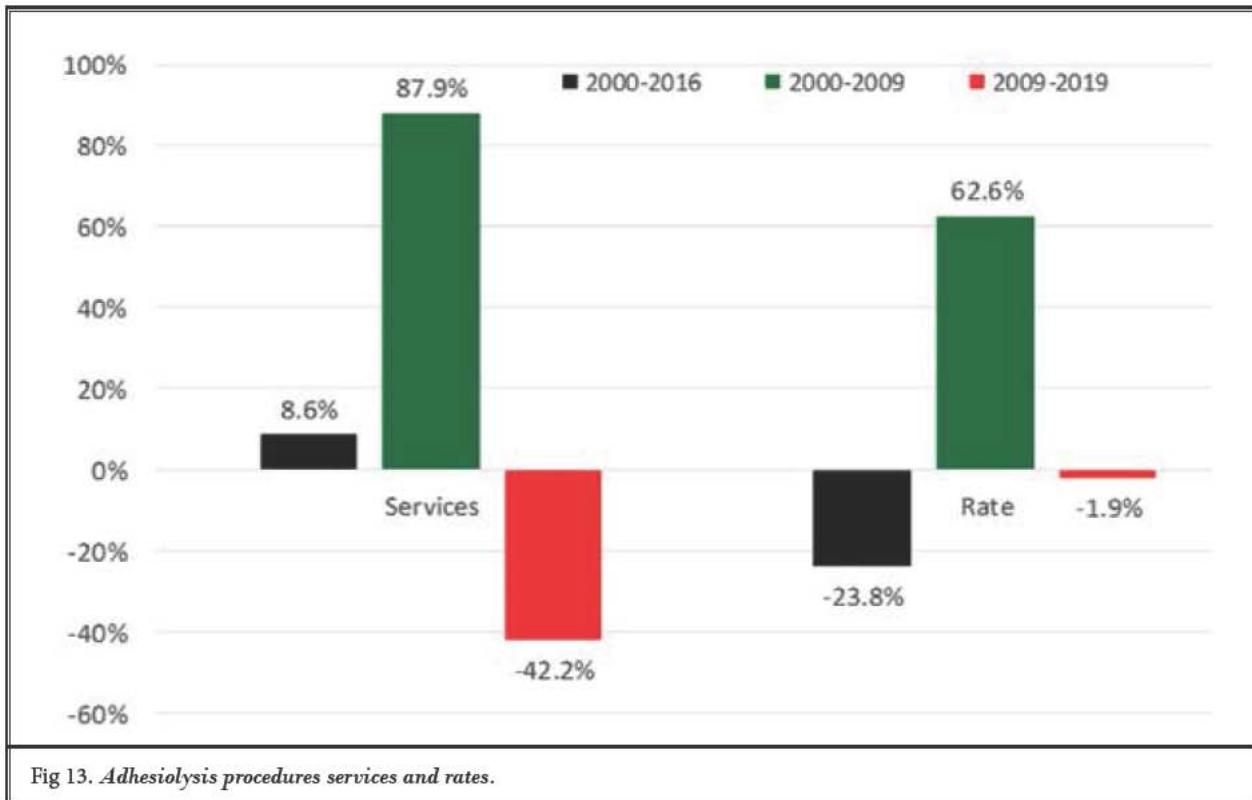
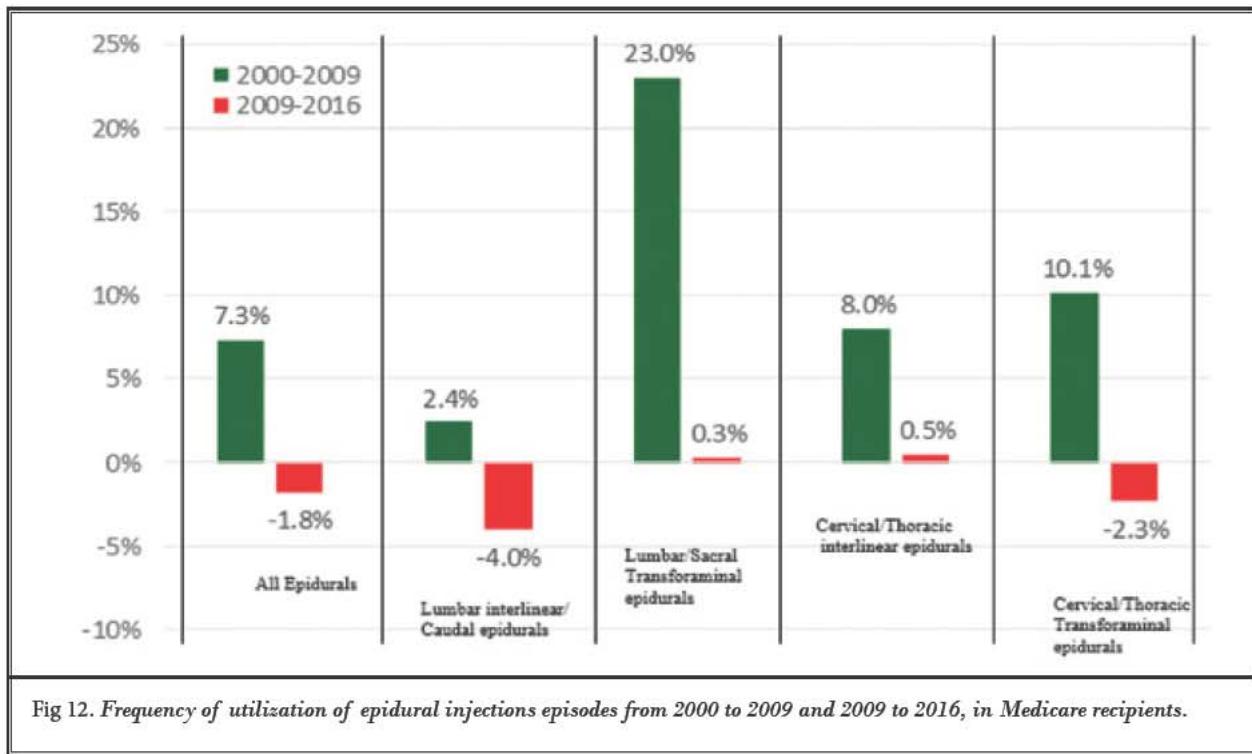
Reframing the Prevention Strategies of the Opioid Crisis

Fig. 9. *Oxycodone consumption, mg/capita.*

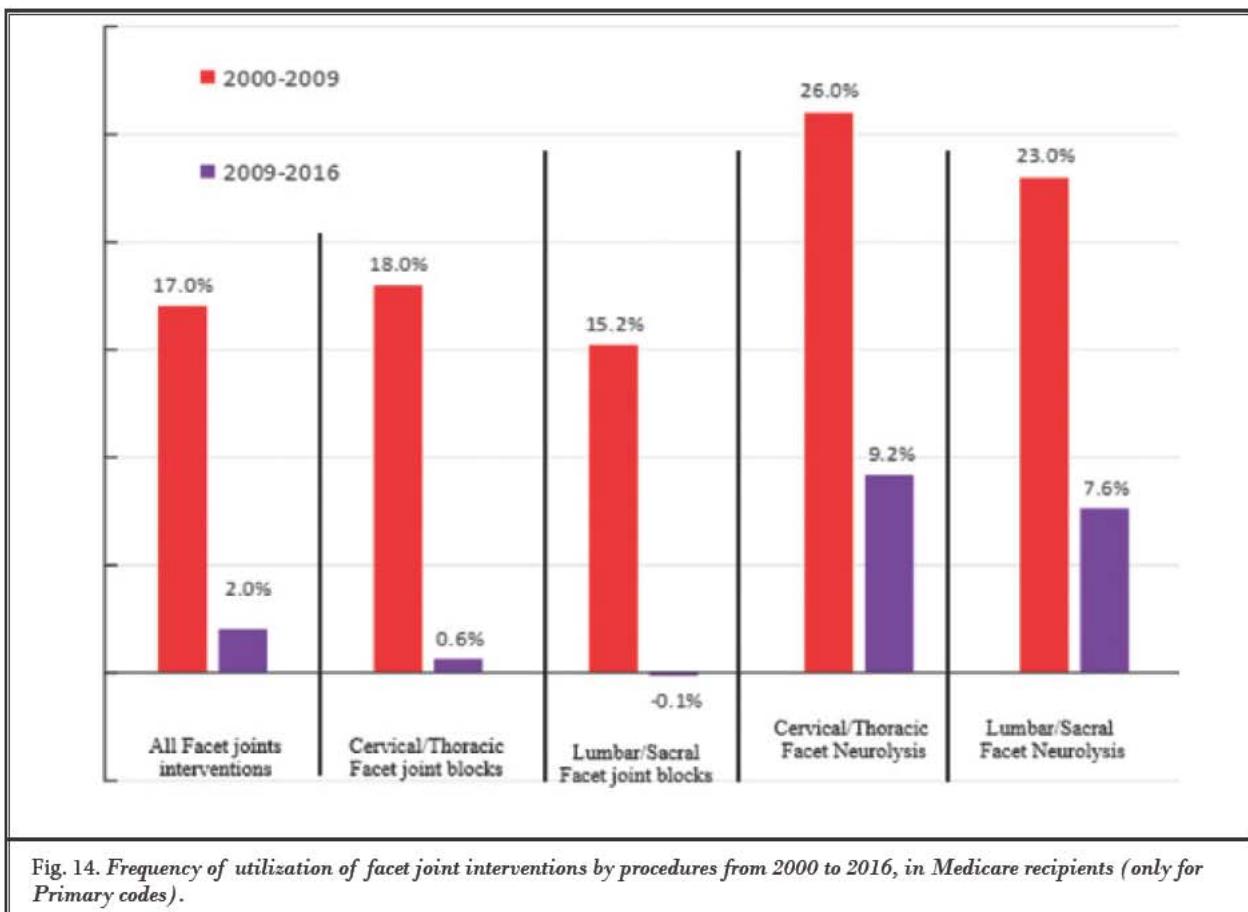
Source: The International Narcotics Control Board. The Conversation, CC-BY-ND

Fig. 10. *Comparison of declining non-medical use of OxyContin versus increasing deaths due to heroin.*Fig. 11. *Comparison of prescription opioid deaths with explosive increase of deaths due to heroin.*

Pain Physician: July/August 2018: 21:309-326



Reframing the Prevention Strategies of the Opioid Crisis



National All Schedules Prescription Electronic Reporting Act (NASPER). NASPER was ultimately signed into law in 2005 as a state-run prescription drug monitoring program (PDMP) (52). As of today, each U.S. state has a PDMP, but barriers to information exchange between the PDMPs of different states exist. Multiple organizations are recommending a national program similar to the NASPER Act. Rather remarkably, NASPER still lacks adequate funding. Further, mandatory provider review of PDMPs and pain clinic laws have been shown to have reduced the amounts of opioids prescribed by 8% and prescription opioid overdose death rates by 12% from 2006–2013. Heroin overdose death rates also declined over this time interval (109–112).

A systematic review by Fink et al (111) assessed 17 studies, 13 on fatal overdoses and 4 on nonfatal overdoses. Three of the 4 nonfatal overdose studies offered insufficient evidence to suggest any conclusions on the effect of PDMP implementation on nonfatal overdoses. Three of the 4 nonfatal overdose studies

offered insufficient evidence to characterize the effect of PDMP implementation on total nonfatal overdoses. Ten of the fatal overdose studies offered low-strength evidence that PDMP implementation reduced total fatal overdoses. The review examined 6 studies on the relationship between PDMP implementation and heroin overdose deaths. Three of the studies found that with PDMP implementation occurred an increase in heroin overdoses. The others found that with PDMP implementation, there was a non-statistically-significant decrease in heroin overdoses (111).

To control the fentanyl and heroin epidemic, one must understand that the majority of the people who use heroin are not seeking fentanyl and essentially are trying to avoid it (71). However, the technology of illicit drug production has advanced to the extent that consumers often cannot correctly identify the products they obtain. Fentanyl in white powder form is in particular difficult to differentiate from other products (72).

Pain Physician: July/August 2018: 21:309-326

Data from patients treated for opioid use disorder collected between 2005 and 2016 ($n = 5,885$) show that 8.7% identified heroin as their initial opioid of use in 2005 compared to 33.3% ($P < 0.001$) in 2015. By contrast, reported use of hydrocodone and oxycodone dropped from approximately 42% to 24.1% and 27.8% respectively in 2015 (73). Another study found an increase in the self-reported use of fentanyl – referred to as “unknown fentanyl products” – from 9% in 2014 to 15% in 2016 among the population entering drug treatment ($n = 10,900$) (74). Consequently, the number of prescription opioid admissions has declined and illicit fentanyl and heroin admissions has increased.

ASIPP 3-Tier Approach to Curb Opioid Abuse

ASIPP aims to curb illicit fentanyl, heroin, and prescription drug abuse while maintaining appropriate access to and proper use of pain management modalities. Consequently, ASIPP has suggested more effective legislation to curb opioid abuse, reducing deaths, while promoting nonopiod modalities such as interventional techniques (26,85-103). Following is the ASIPP three-tier approach toward achieving this goal.

Tier 1

1. Institute an aggressive public education campaign with explicit teaching on the dangers of using illicit drugs, specifically heroin and fentanyl.
2. Institute a public education campaign on opioid abuse in general with emphasis on the adverse consequences of the combined use of opioids and benzodiazepines.
 - The diversity of public opinion, regarding which parties are most responsible for the opioid crisis, is illustrated in Table 1 and Fig. 7 (11,29,30).
3. Implement physician education that excludes the involvement of industry. Make mandatory at least four hours of continuing education per year for each prescriber of any amount of opioids or benzodiazepines.
4. Implement mandatory patient education upon the first prescription of any amount of opioid.

Tier 2

5. Reduce or eliminate copayments to make nonopiod pain management techniques, including physical therapy and interventional procedures, more accessible and improve patient pain and

function outcomes (24,113,114).

- Ironically, as both reimbursements for and utilization of interventional procedures have decreased since 2010, opioid deaths have escalated (85-108). The direct inverse relationship, between the performance of interventional pain procedures and the number of opioid deaths per year, is illustrated in figures 12-14.
- 6. Expand low-threshold access to buprenorphine for opioid use disorder (3,5,115). It has been shown that a substantial proportion of patients who would benefit from buprenorphine treatment will receive this only if it becomes more attractive and more accessible than either prescription or illicit opioids (3).
 - Opioid overdose deaths were shown to decrease by 79% over a period of 6 years after the initiation of widespread buprenorphine prescription in France (115). Expanding low-threshold access will also pave the way toward making buprenorphine and its products available in the management of chronic pain (as described under tier 3).
- 7. Increase the capacity of each state’s PDMP to interact at a minimum with all bordering state PDMPs through the NASPER Act.
- 8. Enforce mandated review of PDMP data prior to all opioid and benzodiazepine prescriptions.

Tier 3

9. Make buprenorphine available as an agent for chronic pain management as well as for medication-assisted treatment. We propose changing the controlled substance classification of buprenorphine from Schedule III to Schedule II to facilitate this.
10. Remove methadone, responsible for over 3,000 deaths per year while comprising only 1% of total opioid prescriptions, from formulary as a listed preferred drug.

CONCLUSION

Americans are facing an opioid crisis of epidemic proportions. It is important to note the degree to which illicit fentanyl and heroin, as well as prescription opioids, contribute to this crisis. This manuscript has discussed numerous factors that have led to this current state – the public’s perception of opioid use, the evolution of the opioid epidemic over the past three

Reframing the Prevention Strategies of the Opioid Crisis

centuries, the influence of greed-based advocacy on the pain movement, failures in the oversight of philanthropy, and the tragic failure of multiple systems that are in place to protect the public due to a confluence of greed. These factors have contributed to misinformation in the development of guidelines and have precipitated ineffective measures by federal, state, and local authorities, governing the use of opioids. Understanding the crisis is critical for providers and policymakers. We have proposed a 3 tier approach toward tackling this scourge.

Acknowledgments

The authors wish to thank Vidyasagar Pampati, MSc, for statistical assistance, and Bert Fellows, MA, Director Emeritus of Psychological Services, for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in the preparation of this manuscript. We would like to thank the editorial board of *Pain Physician* for its review and criticism in improving the manuscript.

REFERENCES

1. Gostin LO, Hodge JG, Noe SA. Reframing the opioid epidemic as a national emergency. *JAMA* 2017; 318:1539-1540.
2. Volkow ND, Collins FS. The role of science in the opioid crisis. *N Engl J Med* 2017; 377:1798.
3. Kolodny A, Frieden TR. Ten steps the federal government should take now to reverse the opioid addiction epidemic. *JAMA* 2017; 318:1537-1538.
4. Bonnie RJ, Kesselheim AS, Clark DJ. Both Urgency and balance needed in addressing opioid epidemic: A report from the National Academies of Sciences, Engineering, and Medicine. *JAMA* 2017; 318:423-424.
5. Dowell D, Noonan RK, Houry D. Underlying factors in drug overdose deaths. *JAMA* 2017; 318:2295-2296.
6. McNeil DG Jr. This flu season is the worst in nearly a decade. *New York Times*, January 26, 2018. <https://www.nytimes.com/2018/01/26/health/flu-rates-deaths.html>
7. Rutkow L, Vernick JS. Emergency legal authority and the opioid crisis. *N Engl J Med* 2017; 377:2512-2514.
8. Glod SA. The other victims of the opioid epidemic. *N Engl J Med* 2017; 376:2101-2102.
9. Gottlieb S, Woodcock J. Marshaling FDA benefit-risk expertise to address the current opioid abuse epidemic. *JAMA* 2017; 318:421-422.
10. Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. *Gen Hosp Psychiatry* 2008; 30:521-527.
11. Blendon RJ, Benson JM. The public and the opioid-abuse epidemic. *N Engl J Med* 2018; 378:407-411.
12. Quenado MA, Volkow ND. Suicide: A silent contributor to opioid-overdose deaths. *N Engl J Med* 2018; 378:1567-1569.
13. Jones CM, Einstein EB, Compton WM. Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016. *JAMA* 2018; 319:1819-1821.
14. Singer JA. Stop calling it an opioid crisis – it's a heroin and fentanyl crisis. *Cato Institute*, January 9, 2018. <https://www.cato.org/blog/stop-calling-it-opioid-crisis-its-heroin-fentanyl-crisis>
15. US Centers for Disease Control and Prevention. Provisional counts of drug overdose deaths as of August 6, 2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf
16. Ingraham C. CDC releases grim new opioid overdose figures: ‘We’re talking about more than an exponential increase.’ *The Washington Post*, December 21, 2017. https://www.washingtonpost.com/news/wonk/wp/2017/12/21/cdc-releases-grim-new-opioid-overdose-figures-were-talking-about-more-than-an-exponential-increase/?utm_term=.f3f893febb8b
17. Guy GP, Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017; 66:697-704.
18. United States Drug Enforcement Administration. DEA proposes reduction to amount of controlled substances to be manufactured in 2018. August 4, 2017. <https://www.dea.gov/divisions/hq/2017/hqo80417.shtml>
19. Schuchat A, Houry D, Guy GP Jr. New data on opioid use and prescribing in the United States. *JAMA* 2017; 318:425-426.
20. Dowell D, Arias E, Kochanek K, Anderson R, Guy GP Jr, Losby JL, Baldwin G. Contribution of opioid-involved poisoning to the change in life expectancy in the United States, 2000-2015. *JAMA* 2017; 318:1065-1067.
21. Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes -- United States, 2017. Surveillance Special Report 1. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. August 31, 2017. <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf>
22. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the epidemic of prescription opioid overdose deaths. *Am J Public Health* 2018; 108:500-502.
23. IQVIA Institute for Human Data Science Study. Medicine use and spending in the U.S. A review of 2017 and outlook for 2022. April 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1527706762033
24. US Burden of Disease Collaborators. The State of US Health, 1990-2016: Burden of Diseases, Injuries, and Risk Factors Among US States. *JAMA* 2018;

Pain Physician: July/August 2018: 21:309-326

- 319:1444-1472.
25. US Burden of Disease Collaborators. The state of US health, 1999-2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.
 26. Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Trescot AM, Blank S, Pampati V, Abdi S, Grider JS, Kaye AD, Manchikanti KN, Cordner HJ, Gharibo CG, Harned ME, Albers SL, Atluri S, Aydin SM, Bakshi S, Barkin R, Benyamin RM, Boswell MV, Buenaventura RM, Calodney AK, Cedeno DL, Datta S, Deer TR, Fellows B, Galan V, Grami V, Hansen H, Helm S 2nd, Justiz R, Koyyalagunta D, Malla Y, Navani A, Nouri K, Pasupuleti R, Sehgal N, Silverman SM, Simopoulos TT, Singh V, Slavin KV, Solanki DR, Staats PS, Vallejo R, Wargo BW, Watanabe A, Hirsch JA. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2017; 20:2S:S3-S92.
 27. Manchikanti L, Atluri S, Hansen H, Benyamin RM, Falco FJE, Helm II S, Kaye AD, Hirsch JA. Opioids in chronic non-cancer pain: Have we reached a boiling point yet? *Pain Physician* 2014; 17:E1-E10.
 28. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep* 2016; 65:1445-1452.
 29. Fry E. Here's who Americans blame most for the opioid epidemic. *Fortune*, June 21, 2017. <http://fortune.com/2017/06/21/opioid-epidemic-blame-doctors/>
 30. Pearl R. Reader survey: Who's responsible for America's opioid epidemic? *Lessons Blog*, January 23, 2018. <http://robertpearlmd.com/survey/>
 31. deShazo R, Johnson M, Eriator I, Rodenmeyer K. Backstories on the U.S. opioid epidemic good intentions gone bad, an industry gone rogue and watch dogs gone to sleep. *Am J Med* 2018 [Epub ahead of print].
 32. Hyams KC, Wignall FS, Roswell R. War syndromes and their evaluation: from the U.S. Civil War to the Persian Gulf War. *Ann Intern Med* 1996; 125:398-405.
 33. United States Drug Enforcement Administration. Controlled Substance Act. <https://www.dea.gov/druginfo/csa.shtml>
 34. U.S. Food and Drug Administration. FDA Public Health Advisory: Methadone Use For Pain Control May Result In Death And Life-Threatening Changes in Breathing and Heartbeat. 2006. http://www.methadone.org/downloads/documents/fda_comsumer_updates_2006_methadone_pain_control_death_changes_breathing_heart_beat_nov_.pdf.
 35. Quinones S. *Dreamland: The True Tale of America's Opiate Epidemic*. Bloomsbury Press, New York, NY, 2015.
 36. Keefe PR. The family that built an empire of pain. *New Yorker*, October 30, 2017. <https://www.newyorker.com/magazine/2017/10/30/the-family-that-built-an-empire-of-pain>
 37. Glueck G. Dr. Arthur Sackler dies at 73; philanthropist and art patron. *New York Times*. <http://www.nytimes.com/1987/05/27/obituaries/dr-arthur-sackler-dies-at-73-philanthropist-and-art-patron.html?mcubz=1>
 38. Porter J, Jick H. A letter to the editor. Addiction rare in patients treated with narcotics. *N Engl J Med* 1980; 302:123.
 39. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; 25:171-186.
 40. Ballantyne J, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003; 349:1943-1953.
 41. Brennan F. The US Congressional "Decade on pain control and research" 2001-2011; a review. *J Pain Palliative Care Pharma* 2015; 29:212-227.
 42. Geriatrics and Extended Care Strategic Healthcare Group National Pain Management Coordinating Committee. Pain as the 5th vital sign toolkit. Department of Veterans Affairs. https://www.va.gov/PAINMANAGEMENT/docs/Pain_As_the_5th_Vital_Sign_Toolkit.pdf.
 43. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring pain as the 5th vital sign does not improve quality of pain management. *J Gen Intern Med* 2006; 21:607-612.
 44. Levine A. How the VA fueled the national opioid crisis and is killing thousands of veterans. *Newsweek*, October 12, 2017. www.newsweek.com/2017/10/20/va-fueled-opioid-crisis-killing-veterans-681552.html
 45. Kozol RA, Voytovich A. Misinterpretation of the fifth vital sign. *JAMA Network* 2007; 298:417-419.
 46. Fauber J. UW a force in pain drug growth. *Milwaukee Journal Sentinel*, April 2, 2011. <http://archive.jsonline.com/watchdog/watchdogreports/119130114.html/>
 47. Joranson DE, Gibson A, Dahl JL, Haddox JD. Pain management, controlled substances, and state medical board policy: A decade of change. *J Pain Symptom Manage* 2002; 23:138-147.
 48. Federation of State Medical Boards of the United States. Position of the Federation of State Medical Boards in Support of Adoption of Pain Management Guidelines. February 23, 2000. <http://www.painpolicy.wisc.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/FSMPwp.pdf>
 49. Federation of State Medical Boards. Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. 2013. <https://license.k3systems.com/LicensingPublic/docs/Model%20Policy-july2013%20FSMB.pdf>
 50. U.S. Drug Enforcement Administration, Agency Details. <https://www.usa.gov/federal-agencies/drug-enforcement-administration>
 51. Drug Enforcement Administration. DEA to join pain advocates in issuing statement on prescription pain medicine. United States Drug Enforcement Administration. 2001. <https://www.dea.gov/pubs/pressrel/pr102301.html>
 52. Manchikanti L, Whitfield E, Pallone F. Evolution of the National All Schedules Prescription Electronic Reporting Act (NASPER): A public law for balancing treatment of pain and drug abuse and diversion. *Pain Physician* 2005; 8:335-347.
 53. Temple J. *American Pain*. First Lyons Press, Gilford, CO, 2016 pp 37-56.
 54. Chou R, Huffman LH; American Pain Society; American College of Physicians. Medications for acute and chronic low back pain: A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147:505-514.
 55. United States Senator Claire McCaskill. BREAKING: Millions in Payments Among Findings of McCaskill Opioid Investigation into Ties Between Manufacturers and Third Party Advocacy Groups. February 12, 2018. <https://www.mccaskill.senate.gov/media-center/news-releases/breaking-millions-in-payments-among-findings-of-mccaskill-opioid-investigation-into-ties-between-manufacturers-and-third-party-advocacy-groups>
 56. Fauber J. Past investigations exposed links between drug companies, push for use of opioids. *Milwaukee Journal Sentinel*, January 28, 2018. <https://www.jsonline.com/story/news/investiga>

Reframing the Prevention Strategies of the Opioid Crisis

- tions/2018/01/28/past-investigations-exposed-links-between-drug-companies-push-use-opioids/1069161001/
57. Higham S, Bernstein L. The drug industry's triumph over the DEA. *The Washington Post*, October 15, 2017. https://www.washingtonpost.com/graphics/2017/investigations/dea-drug-industry-congress/?utm_term=.7754e7332099
58. McVeigh K. US drug agency surveillance unit to be investigated by Department of Justice. *The Guardian*, August 6, 2013. <https://www.theguardian.com/world/2013/aug/06/justice-department-surveillance-dea>.
59. Mitchell J. How the FDA helped pave the way for an opioid epidemic. *Clarion Ledger*, January 26, 2018. <https://www.clarionledger.com/story/news/2018/01/26/opioid-epidemic-how-fda-helped-pave-way/950561001/>
60. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA* 2018; 319:872-882.
61. Manchikanti L, Atluri S, Candido KD, Boswell MV, Simopoulos TT, Grider JS, Falco FJE, Hirsch JA. Zohydro™ approval by Food and Drug Administration: Controversial or frightening? *Pain Physician* 2014; 17:E437-E450.
62. Pizzo PA, Clark NM. Alleviating suffering 101 – pain relief in the United States. *N Engl J Med* 2012; 366:197-199.
63. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.
64. Zee AV. The promotion and marketing of OxyContin: Commercial Triumph, Public Health Tragedy. *AJPH* 2009; 99:221-227.
65. Kolodny A. The opioid epidemic in 6 charts. *The Conversation*, October 4, 2017. <https://theconversation.com/the-opioid-epidemic-in-6-charts-81601>
66. Bloom J. The opioid epidemic in 6 charts designed to deceive you. *American Council on Science and Health*, October 12, 2017. <https://www.acsh.org/news/2017/10/12/opioid-epidemic-6-charts-designed-deceive-you-11935>
67. Mandal A. Fentanyl history. *News Medical Life Sciences*, July 3, 2014. <https://www.news-medical.net/health/Fentanyl-History.aspx>.
68. Tribune News Services. More than 50,000 overdose deaths: A grim tally soars to all-time U.S. high. *Chicago Tribune*, December 8, 2016. <http://www.chicagotribune.com/news/nationworld/ct-us-overdose-deaths-20161208-story.html>.
69. U.S. Drug Enforcement Administration. DEA issues carfentanil warning to the police and public. September 22, 2016. <https://www.dea.gov/divisions/hq/2016/hq092216.shtml>
70. US Food and Drug Administration. FDA drug safety communication: FDA warns about serious risks and deaths when combining opioid pain or cough medications with benzodiazepines; requires its strongest warning. September 20, 2017. www.fda.gov/Drugs/DrugSafety/ucm518473.htm
71. Carroll JJ, Marshall BDL, Rich JD, Green TC. Exposure to fentanyl-contaminated heroin and overdose risk among illicit opioid users in Rhode Island. *Int J Drug Policy* 2017; 46:136-145.
72. Gladden RM, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths. *MMWR Morb Mortal Wkly Rep* 2016; 65:837-843.
73. Cicero TJ, Ellis MS, Kasper ZA. Increased use of heroin as an initiating opioid of abuse. *Addict Behav* 2017; 74:63-66.
74. Cicero TJ, Ellis MS, Kasper ZA. Increases in self-reported fentanyl use among a population entering drug treatment: The need for systematic surveillance of illicitly manufactured opioids. *Drug Alcohol Depend* 2017; 177:101-103.
75. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Reversal of growth of utilization of interventional techniques in managing chronic pain in Medicare population post Affordable Care Act. *Pain Physician* 2017; 20:551-567.
76. Manchikanti L, Pampati V, Hirsch JA. Retrospective cohort study of usage patterns of epidural injections for spinal pain in the US fee-for-service Medicare population from 2000 to 2014. *BMJ Open* 2016; 6:e013042.
77. Manchikanti L, Hirsch JA, Pampati V, Boswell MV. Utilization of facet joint and sacroiliac joint interventions in Medicare population from 2000 to 2014: Explosive growth continues! *Curr Pain Headache Rep* 2016; 20:58.
78. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Comparative analysis of utilization of epidural procedures in managing chronic pain in the Medicare population: Pre and post Affordable Care Act. *Spine (Phila Pa 1976)* 2018; in submission.
79. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Comparative retrospective cohort study of utilization patterns of facet joint interventions in managing spinal pain in the Medicare population: Pre- and post-Affordable Care Act. *BMJ Open* 2018; in submission.
80. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Declining utilization of percutaneous epidural adhesiolysis in Medicare population: Evidence-based or over-regulated? *IPM Reports* 2018; 2:9-18.
81. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Cost calculation methodology exacerbates site-of-service differentials by 10- to 18-fold for soft tissue and joint injections in hospital outpatient departments. *IPM Reports* 2017; 1:183-189.
82. Manchikanti L, Pampati V, Hirsch JA. Usage patterns of sacroiliac joint injections - a comparative evaluation of pre and post Affordable Care Act in Medicare Population. *IPM Reports* 2018; in submission.
83. Manchikanti L, Kaye AD, Hirsch JA. Proposed Medicare physician payment schedule for 2017: Impact on interventional pain management practices. *Pain Physician* 2016; 19:E935-E955.
84. Manchikanti L, Singh V, Hirsch JA. Facility payments for interventional pain management procedures: Impact of proposed rules. *Pain Physician* 2016; 19:E957-E984.
85. Manchikanti L, Benyamin RM, Falco FJ, Kaye AD, Hirsch JA. Do epidural injections provide short- and long-term relief for lumbar disc herniation? A systematic review. *Clin Orthop Relat Res* 2015; 473:1940-1956.
86. Manchikanti L, Staats PS, Nampiaparampil DE, Hirsch JA. What is the role of epidural injections in the treatment of lumbar discogenic pain: A systematic review of comparative analysis with fusion and disc arthroplasty. *Korean J Pain* 2015; 28:75-87.
87. Manchikanti L, Kaye AD, Manchikanti KN, Boswell MV, Pampati V, Hirsch JA. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: A systematic review. *Anesth Pain Med* 2015; 5:e23139.
88. Manchikanti L, Manchikanti KN, Ghario CG, Kaye AD. Efficacy of percutaneous adhesiolysis in the treatment of lumbar post surgery syndrome. *Anesth*

Pain Physician: July/August 2018: 21:309-326

- Pain Med 2016; 6:e26172.
89. Helm IL S, Racz GB, Gerdesmeyer L, Justiz L, Hayek SM, Kaplan ED, El Terany MA, Knezevic NN. Percutaneous and endoscopic adhesiolysis in managing low back and lower extremity pain: A systematic review and meta-analysis. *Pain Physician* 2016; 19:E245-E282.
 90. Boswell MV, Manchikanti L, Kaye AD, Bakshi S, Gharibo CG, Gupta S, Jha S, Nampiaparampil DE, Simopoulos TT, Hirsch JA. A best-evidence systematic appraisal of the diagnostic accuracy and utility of facet (zygapophysial) joint injections in chronic spinal pain. *Pain Physician* 2015; 18:E497-E533.
 91. Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, Grider JS, Gupta S, Jha S, Mann DP, Nampiaparampil DE, Sharma ML, Shroyer LN, Singh V, Soin A, Vallejo R, Wargo BW, Hirsch JA. A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain. *Pain Physician* 2015; 18:E535-E582.
 92. Simopoulos TT, Manchikanti L, Gupta S, Aydin SM, Kim CH, Solanki D, Nampiaparampil DE, Singh V, Staats PS, Hirsch JA. Systematic review of the diagnostic accuracy and therapeutic effectiveness of sacroiliac joint interventions. *Pain Physician* 2015; 18:E713-E756.
 93. Grider JS, Manchikanti L, Carayannopoulos A, Sharma ML, Balog CC, Harned ME, Grami V, Justiz R, Nouri KH, Hayek SM, Vallejo R, Christo PJ. Effectiveness of spinal cord stimulation in chronic spinal pain: A systematic review. *Pain Physician* 2016; 19:E33-E54.
 94. Helm S 2nd, Simopoulos TT, Stojanovic MP, Abdi S, El Terany MA. Effectiveness of thermal annular procedures in treating discogenic low back pain. *Pain Physician* 2017; 20:447-470.
 95. Li X, Wang R, Xing X, Shi X, Tian J, Zhang J, Ge L, Zhang J, Li L, Yang K. Acupuncture for myofascial pain syndrome: A network meta-analysis of 33 randomized controlled trials. *Pain Physician* 2017; 20:E883-E902.
 96. Yang JS, Zeng YS, Liu TJ, Hao DJ. Full-endoscopic procedures versus traditional discectomy surgery for discectomy: A systematic review and meta-analysis of current global clinical trials. *Pain Physician* 2017; 20:E1123-E1124.
 97. Xing XF, Zhou ZF, Zhang FJ, Yan M. The effect of early use of supplemental therapy on preventing postherpetic neuralgia: A systematic review and meta-analysis. *Pain Physician* 2017; 20:471-486.
 98. Xu Q, Chen B, Wang Y, Wang X, Han D, Ding D, Zheng Y, Cao Y, Zhan H, Zhou Y. The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: A systematic review and meta-analysis. *Pain Physician* 2017; 20:229-243.
 99. Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS. Electric stimulation for pain relief in patients with fibromyalgia: A systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2017; 20:15-25.
 100. Kregel J, Coppieters I, DePauw R, Malfliet A, Danneels L, Nijs J, Cagnie B, Meeus M. Does conservative treatment change the brain in patients with chronic musculoskeletal pain? A systematic review. *Pain Physician* 2017; 20:139-154.
 101. Chang KV, Wu WT, Hung CY, Han DS, Yang RS, Chang CH, Lin CP. Comparative Effectiveness of suprascapular nerve block in the relief of acute post-operative shoulder pain: A systematic review and meta-analysis. *Pain Physician* 2016; 19:445-456.
 102. Sun H, Lu PP, Liu YJ, Yang X, Zhou PH, Shen XF, Sun SW, Yang H. Can unilateral kyphoplasty replace bilateral kyphoplasty in treatment of osteoporotic vertebral compression fractures? A systematic review and meta-analysis. *Pain Physician* 2016; 19:551-563.
 103. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural Injections for lumbar radiculopathy and spinal stenosis: A comparative systematic review and meta-analysis. *Pain Physician* 2016; 19:E365-410.
 104. Manchikanti L, Falco FJE, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. *Pain Physician* 2013; 16:E129-E143.
 105. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Cost utility analysis of lumbar interlaminar epidural injections in the treatment of lumbar disc herniation, central spinal stenosis, and axial or discogenic low back pain. *Pain Physician* 2017; 20:219-228.
 106. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Therapeutic lumbar facet joint nerve blocks in the treatment of chronic low back pain: Cost utility analysis based on a randomized controlled trial. *Korean J Pain* 2018; 31:27-38.
 107. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Cost utility analysis of cervical therapeutic medial branch blocks in managing chronic neck pain. *Int J Med Sci* 2017; 14:1307-1316.91
 108. Farber SH, Han JL, Elsamadicy AA, Hussaini Q, Yang S, Pagadala P, Parente B, Xie J, Lad SP. Long-term cost utility of spinal cord stimulation in patients with failed back surgery syndrome. *Pain Physician* 2017; 20:E797-E805.
 109. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. *Health Aff (Millwood)* 2016; 35:1876-1883.
 110. Bao Y, Pan Y, Taylor A, Radakrishnan S, Luo F, Pincus HA, Schackman BR. Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Aff (Millwood)* 2016; 35:1045-1051.
 111. Fink DS, Schleimer JP, Sarvet A, Grover KK, Delcher C, Castillo-Carniglia A, Kim JH, Rivera-Aguirre AE, Henry SG, Martins SS, Cerdá M. Association between prescription drug monitoring programs and nonfatal and fatal drug overdoses. *Ann Intern Med* 2018 [Epub ahead of print].
 112. Compton WM, Wargo EM. Prescription drug monitoring programs: Promising practices in need of refinement. *Ann Intern Med* 2018 [Epub ahead of print].
 113. Testimony of Ramsin Benyamin, MD, Before the Ways and Means Committee, US House of Representatives, February 6, 2018.
 114. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther* 2018 [Epub ahead of print].
 115. Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, Tignol J. French field experience with buprenorphine. *Am J Addict* 2004; 13:S17-S28.